EXHIBIT G

Mesh shrinkage:
How to assess, how to prevent, how to manage ?

WORKSHOP #2
Postoperative specific complications following transvaginal mesh repair of pelvic organ prolapse: etiology, prevention and management.

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What is mesh shrinkage ?

- **Definition**
  - **Reduction of the mesh area after tissue incorporation**
  - Synonyma: retraction, contraction
  - Often associated with mesh thickening and folding
- **A phenomenon**
  - Well-documented in animal studies (range 15-65%)
  - Experienced by abdominal surgeon
  - **Wich has become a raising concern in urogynecology since the widespread use of vaginal mesh**

What did we learn from abdominal wall repair studies?

- **Mesh repair**
  - **Reduce the rate of recurrence** compared with traditional suture repair
  - Works by both direct mechanical sealing (sublay) and induction of a scar plate formation
- **Several complications** associated with the use of mesh may be due to the **chronic inflammatory reaction** to the mesh or **a loss of compliance after degradation of the material**
- **Mesh shrinkage**, folding and migration, may result in some cases in a **recurrent hernia** and also **pain**

Amid PK, Hernia 1997
LeBlanc KA, Hernia 2001

What is specific to vaginal surgery ?

- Much of what we know about grafts comes from research involving the abdominal wall hernias
- Poor knowledge of the vaginal in vivo response to the materials
- The vagina has an important vascularity and endogenous microflora that may have an impact on host tissue response and biomechanical properties of grafts used in pelvic reconstructive

What do we observe with mesh repair in our field ?

- **It improves the anatomical outcome**
  - L1 evidence for anterior compartment
  - Numerous series with encouraging data on apical and posterior compartment

Jia X, BJOG 2008

- **Mesh shrinkage may be associated with**
  - Stiffness/tenderness at vaginal examination
  - Discomfort/pain during intercourses
  - Pelvic pain
  - Urinary or defecatory dysfunction
  - Prolapse recurrence

Margulies RU, AJOG 2008
Boyles SH, Obstet Gynecol 2008
Velemir L, Ultrasound Obstet Gynecol 2009 (in press)

Why does mesh shrinkage happen ?

- **An unclear etiology**
- **Shrinkage** should not be considered as a complication of the biomaterial but as a **a consequence of the incorporation of the mesh to a scar tissue**
- **Biomaterials (even PP) are not inert !**

Klinge U, Eur J Surg 1999

Histological sequence after mesh incorporation

Immediatly, **immunological stimulus**

Binding of proteins to the mesh surface with attraction and immigration of macrophages and fibroblasts

First days, **inflammatory phase**

Within 1-3 weeks, **wound contraction**

Scar tissue build up by fibroblasts with abundant collagen deposition
Typical granuloma surrounding the mesh
Wound contraction by myofibroblasts with large bundles of actin microfilaments

Mesh contraction essentially takes place during the first 2 months

However some observations support the idea of a chronic inflammation which persists several years

Ferrando JM, World J Surg 2002

Kapischke M, Surg Endosc 2005

Frequence of mesh shrinkage

- Unknown !
  - Prolift database : 25 studies ; 3322 patients, **range 0-17%**

- Clinical relevance of mesh shrinkage ?
  - Always a certain degree of mesh shrinkage
  - Asymptomatic in most cases

- Need for a better screening during patient follow-up
  - Prospective assessment ++
  - Rigorous methodology
  - Validated questionnaire
  - Standardized tools

How to assess mesh shrinkage ?

Clinical assessment

- Transvaginal palpation of the mesh
  - Estimation of the percentage of mesh dimensions (lenght/wide) decrease compared to original mesh dimensions
- VAS of vaginal pain
  - Spontaneous pain
  - During examination only
- Assessment of sexual outcome
- Use of specific classification

Reproducibility ?

Debodinance et al, Synthetic meshes for transvaginal surgical cure of genital prolapse: evaluation in 2005. J Gynecol Obstet Biol Reprod 2006

Type 3 complication: mesh shrinkage

- *Grade 1 : mesh palpable but no sensitive*

(moderate asymptomatic shrinkage)

** Grade 2 : moderate shrinkage and/or little symptomatic*

(tenderness at palpation, thickenning without mesh node)

** Grade 3 : severe shrinkage and/or symptomatic with sensitive palpation*

(local mesh thickening)

** Grade 4 : painful mesh palpation*

Mesh shrinkage classification: suggestion from M.Cosson and B.Fatton

UIGA Annual meeting Tai Pei, 2008

Grade			
1	asymptomatic		Degree of retraction A : < 50% B : > 50%
2	Provoked pain only (during vaginal examination)		
3	dyspareunia	Occasionally: + Usually: ++ Always: +++	
4	Pain during physical activities	Occasionally: + Usually: ++ Always: +++	
5	Spontaneous pain	Occasionally: + Usually: ++ Always: +++	

Our experience

- Prospective control of 107 patients operated between march 2005 and august 2006 for symptomatic stage 2-4 cystocele and/or rectocele with Prolift
  - 56 total Prolift including 20 in two pieces and 36 monobloc
  - 33 anterior Prolift
  - 18 posterior Prolift
- Transvaginal mesh palpation
  - Mesh shrinkage (%)
  - Triggerred tenderness (VAS)

Results

	Anterior mesh (n=89)	Intermediate part (n=20)	Posterior mesh (n=74)
n shrinked mesh (%)	78 (**87.6**)	13 (**65**)	43 (**58.1**)
Mean shrinkage % (range)	**24.4** (0-75)	NA	**15.5** (0-70)
n tenderness at palpation (%)	14 (**15.7**)	5 (**25**)	10 (**13.5**)
Mean VAS in case of tenderness (range)	4.6 (2-9)	5.8 (4-8)	4.8 (2-7)

A mean 15-25% of shrinkage was perceived in 60 to 90% of cases

Clinical impact of mesh shrinkage

- Spontaneous pelvic/perineal pain related to severe mesh shrinkage present in 3 patients (2.8 %) with a mean VAS of 5/10
- Tenderness/pain at vaginal examination associated with mesh shrinkage present in 21 patients (19,6%) with a mean VAS of 5/10

=> 13 patients sexually active

- 8 patients without dyspareunia
- 4 patients with unchanged dyspareunia compared to preoperative status
- 1 patient with *de novo* dyspareunia

=> 8 patients sexually inactive including 1 because of *de novo* dyspareunia

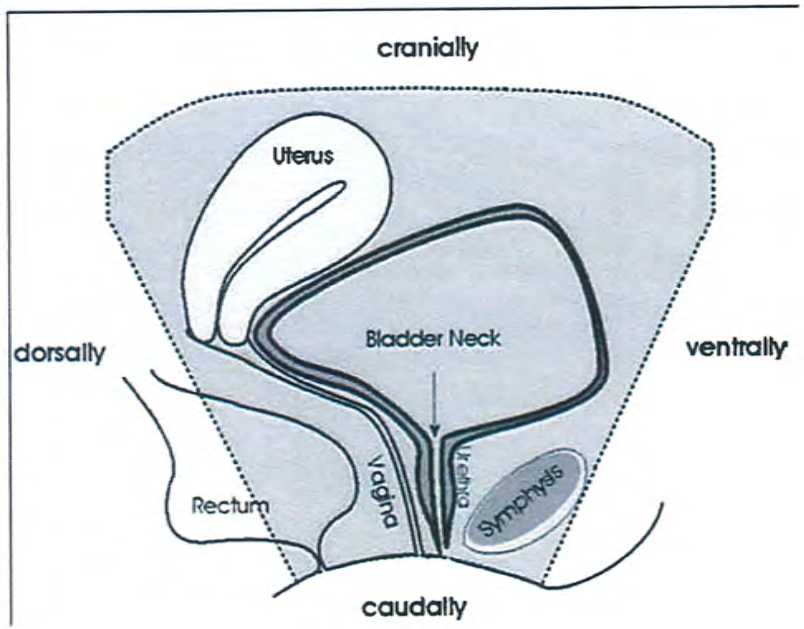
How to assess ?

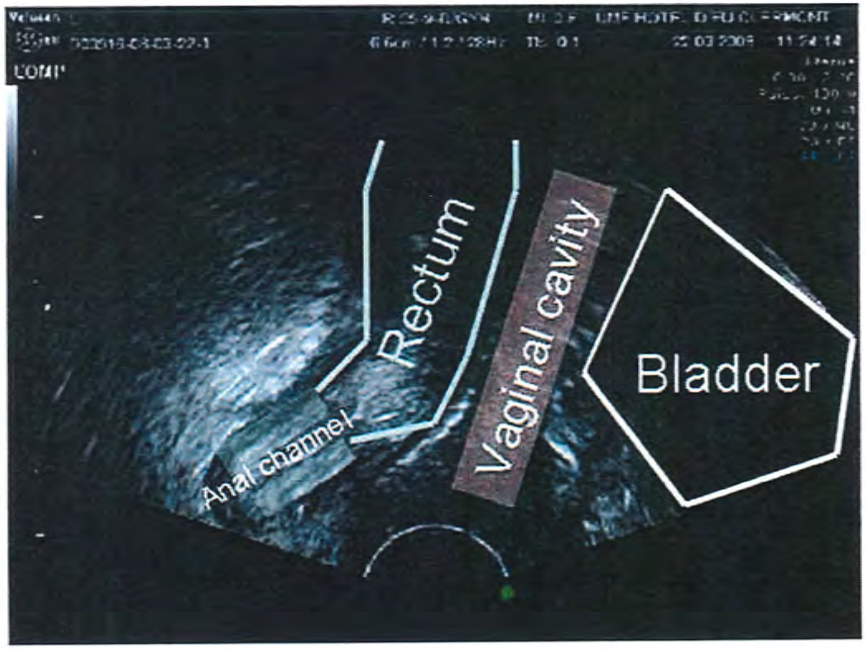
Ultrasonography

- Transvaginal introital ultrasound
- Accessible
- Reproducible
- Objective measurement of
  - Mesh length
  - Mesh configuration
  - Mesh thickness
- Better understanding of
  - Recurrence
  - Postoperative pain or dyspareunia

Is there any correlation beetween US measurements and anatomical and/or functional outcomes ?

Landmarks for UroGyn ultrasound

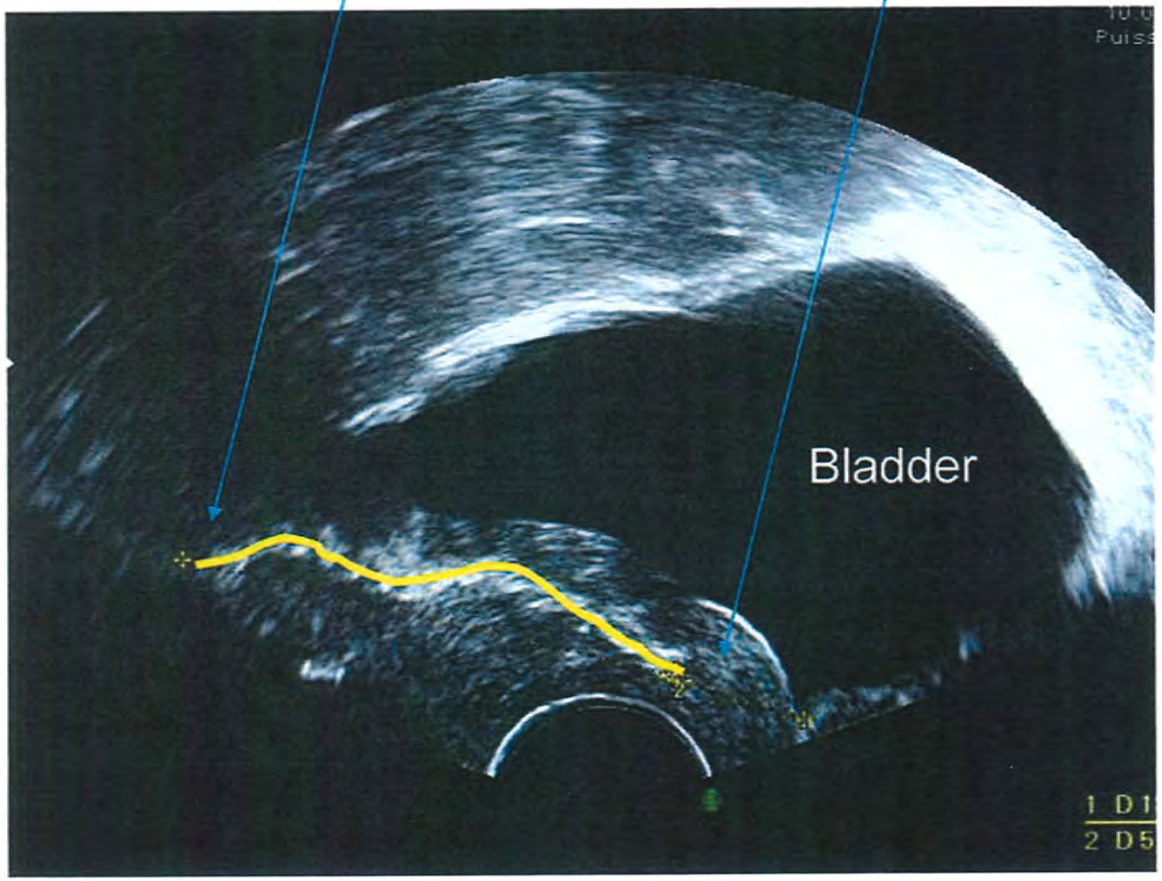


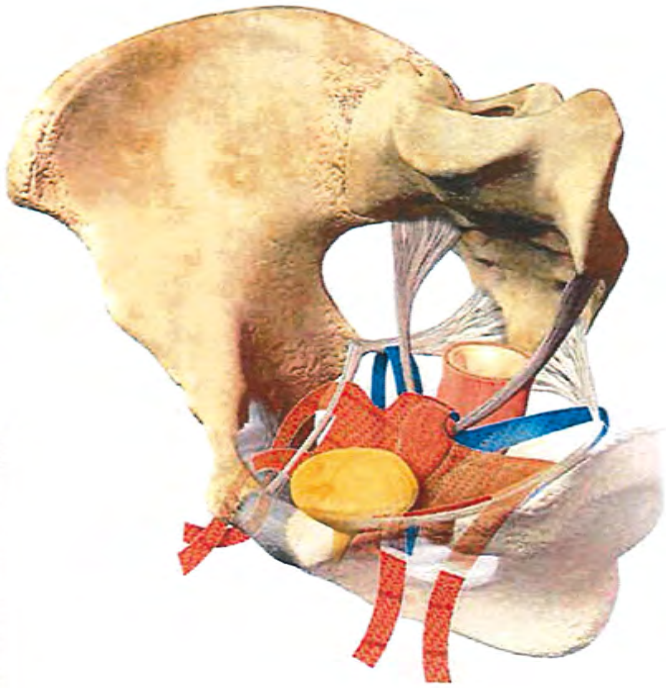


Tunn R, Int Urogynecol J 2005

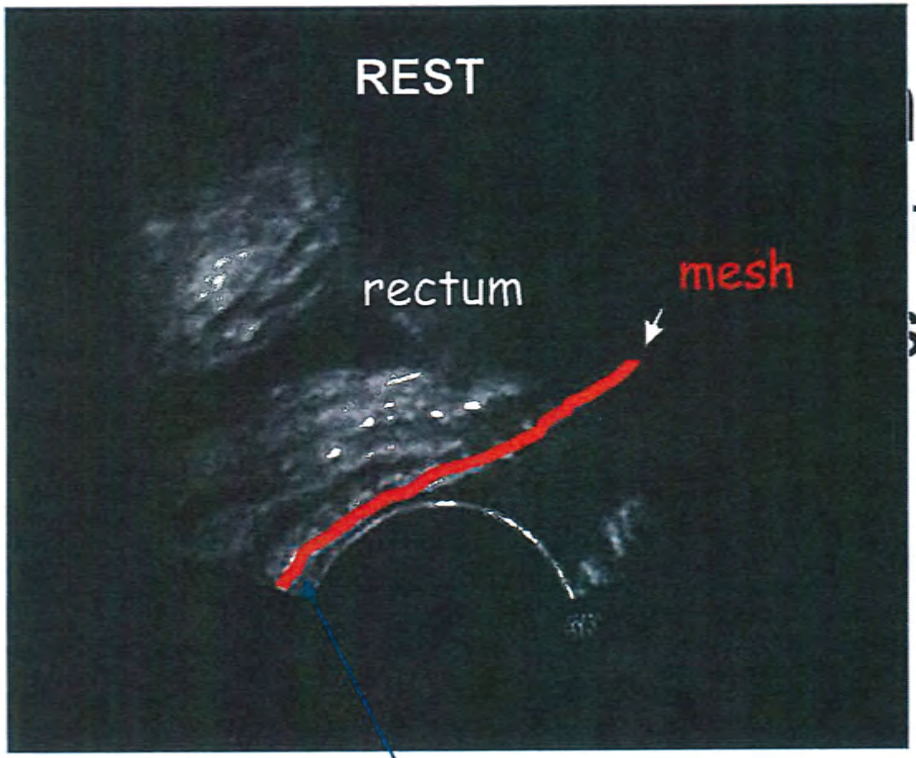
Anterior mesh

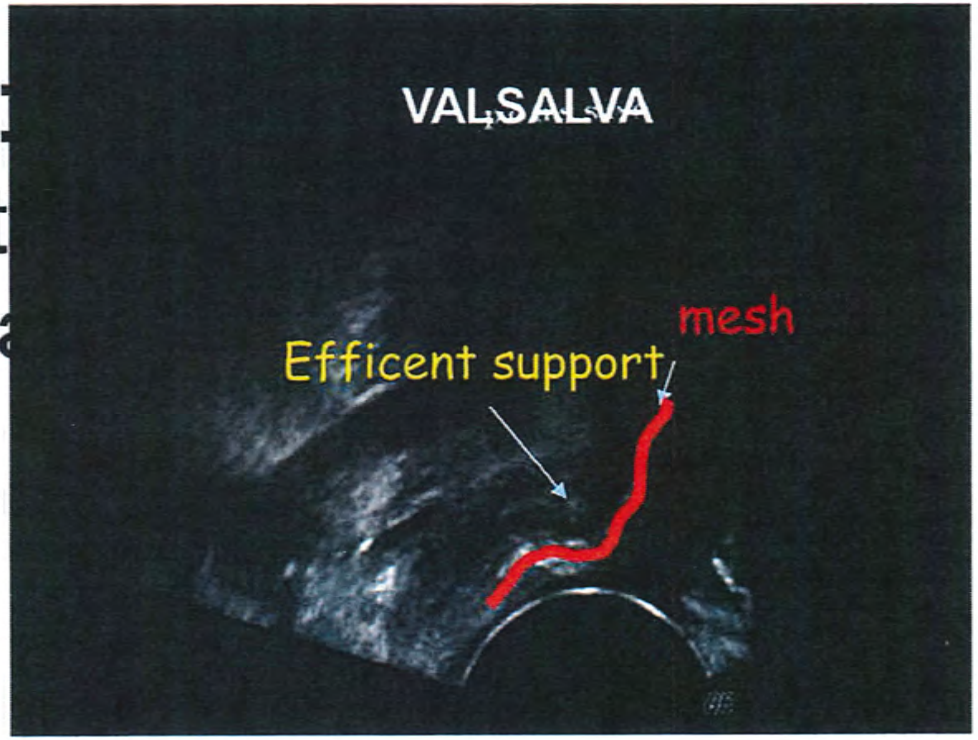
Support of the anterior vaginal wall from the ischial spine to the bladder neck





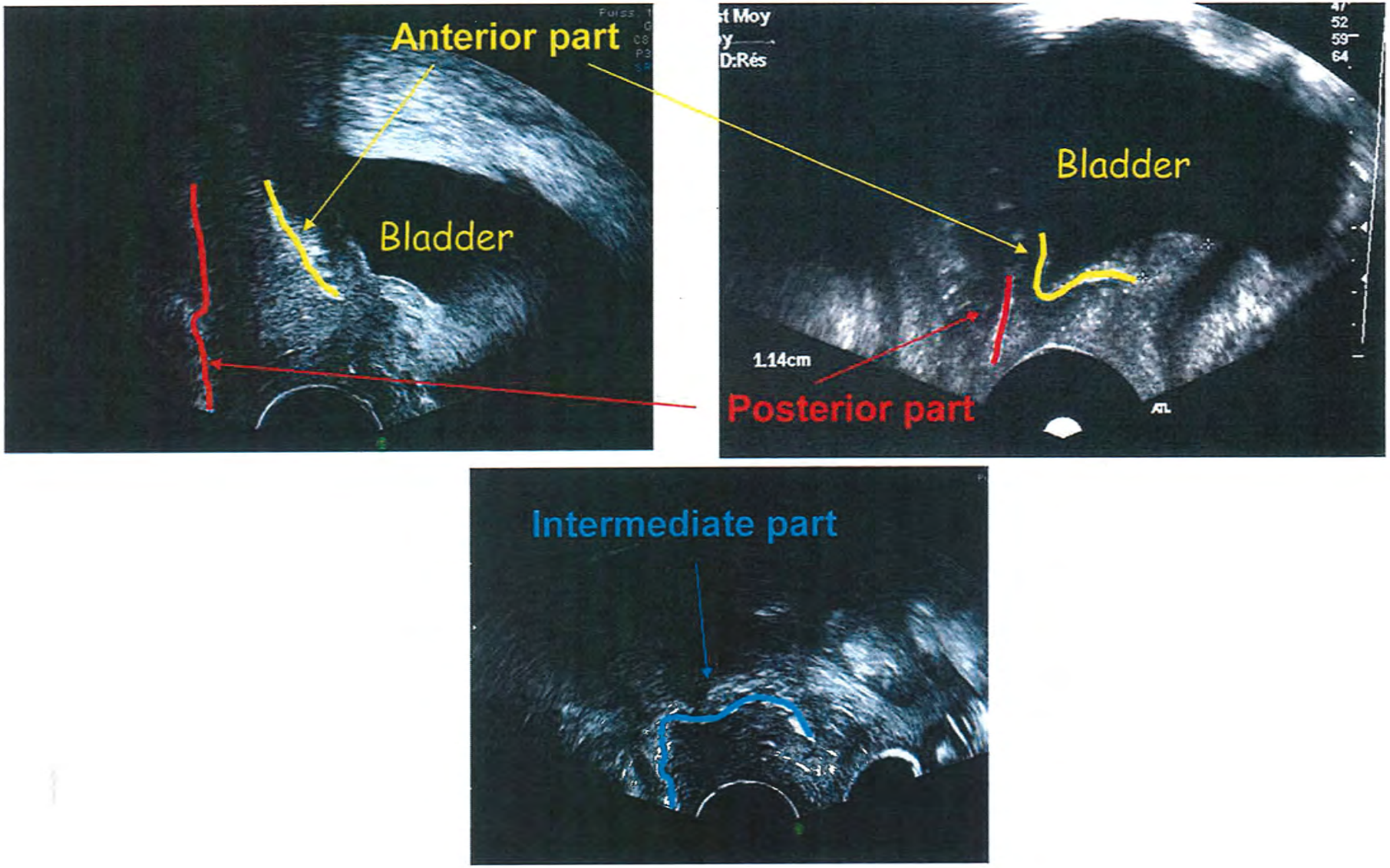
Posterior mesh





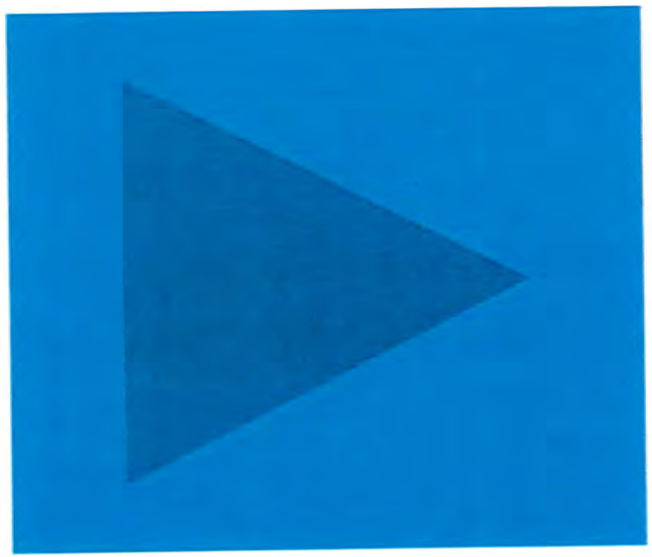
Note that the mesh comes down to the perineum

Total monobloc mesh

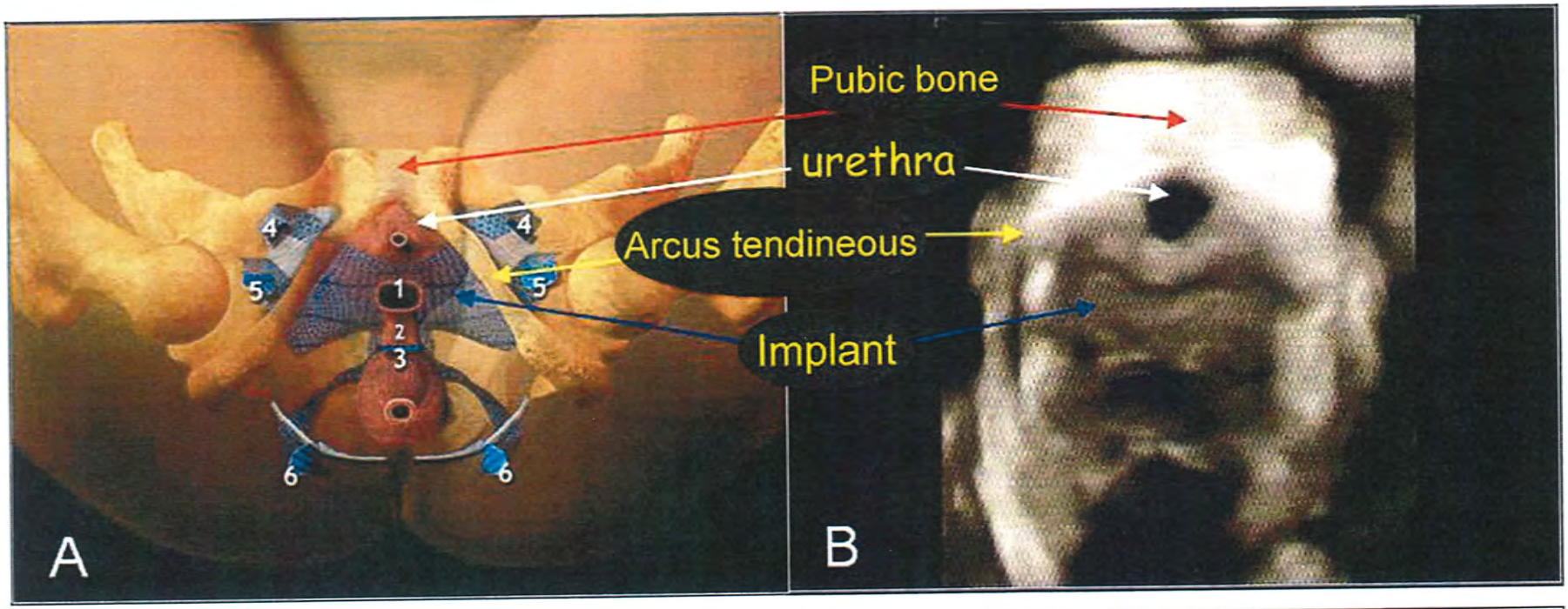


Video 1

Sonographic assessment of a total monobloc prolift®



Transobturator mesh in 3D



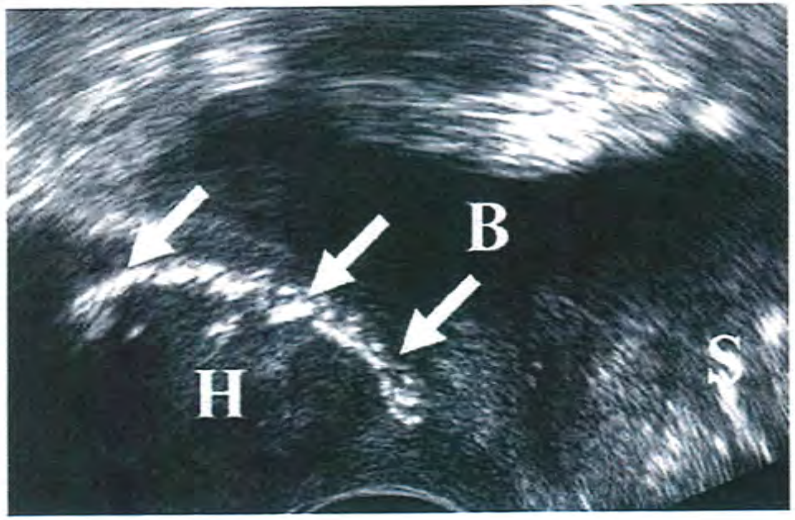
Courtesy of D.Lemery, MD

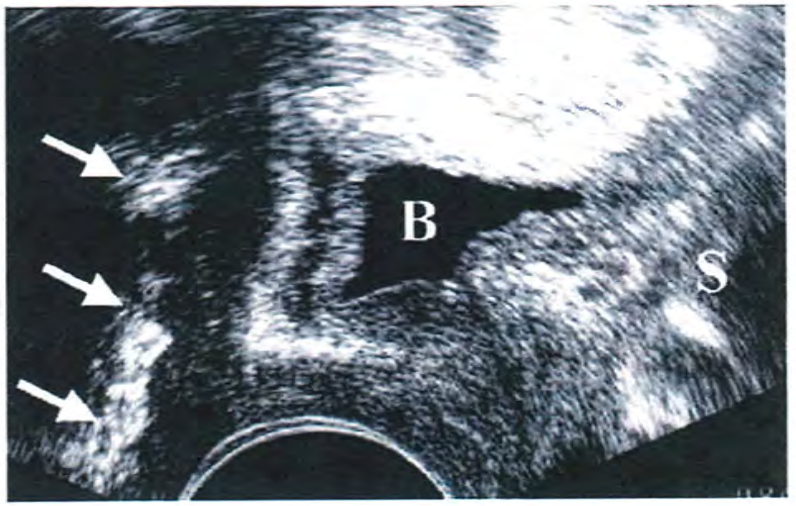
Ultrasound Obstet Gynecol 2007; 29: 449–452
Published online 1 March 2007 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/uog.3962

Sonomorphological evaluation of polypropylene mesh implants after vaginal mesh repair in women with cystocele or rectocele

R. TUNN, A. PICOT, J. MARSCHKE and A. GAURUDER-BURMESTER
Department of Urogynecology, German Pelvic Floor Center, St. Hedwig Hospitals, Berlin, Germany

Comparison of the initial length of the mesh implanted and the sonographically measured length of the mesh 6 weeks postoperatively





Length of implanted mesh evaluated by US

Results

Tunn R, Ultrasound Obstet Gynecol, 2007

Table 1 Length of mesh at implantation and at postoperative sonographic follow-up

Mesh type	Mesh length (cm, mean ± SD)		Post op mesh length as % of initial length	% of vaginal length supported by mesh
	at implantation*	postoperatively		
Transobturator (cystocele)	6.8 ± 1.1	2.9 ± 0.6	43.2	43.4
Perigee	6.4 ± 1.2	2.9 ± 0.6	45.4	43.7
Prolift Anterior	7.5 ± 0.4	3.0 ± 0.8	39.3	42.9
Transischioanal (rectocele)	9.9 ± 0.8	3.3 ± 0.5	33.6	53.7
Apogee	10.3 ± 0.7	3.4 ± 0.6	32.8	55.5
Prolift Posterior	9.1 ± 0.4	3.2 ± 0.4	35.2	50.3

*Initial mesh length (adjusted intraoperatively by the operator).

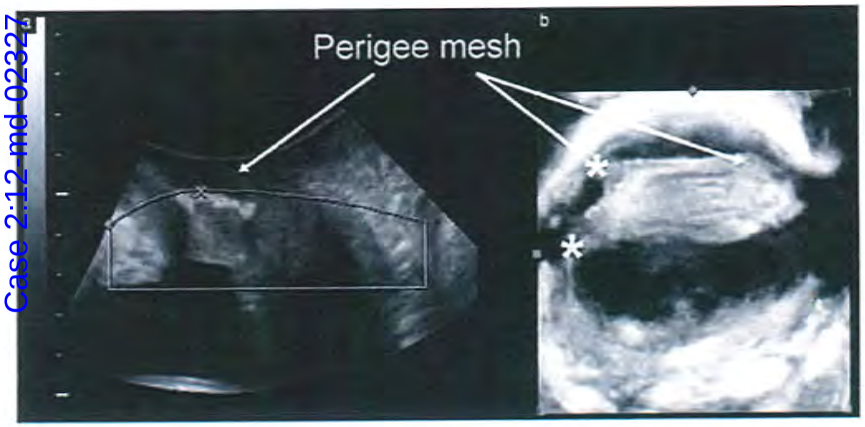
- Decrease of the length size of 60% for the anterior mesh and of 65% for the posterior mesh.
- The mesh supported 40% of the length of the anterior vaginal wall and 50% for the posterior mesh.

Ultrasound Obstet Gynecol 2008; 32: 82–86
Published online 10 June 2008 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/uog.5361

Transobturator mesh for cystocele repair: a short- to medium-term follow-up using 3D/4D ultrasound

K. L. SHEK*, H. P. DIETZ*, A. RANE† and S. BALAKRISHNAN†
*Nepean Clinical School, University of Sydney, Penrith and †James Cook University, Townsville, Australia

- 46 patients with transobturator anterior mesh
- ICS POP Q + 3D-4D translabial US



Patient with good clinical result
- Mesh well spread out
- Minimal folding
- Both effective anchoring arms

Results

Shek KL, Ultrasound Obstet Gynecol, 2008

Follow-up: 10 months

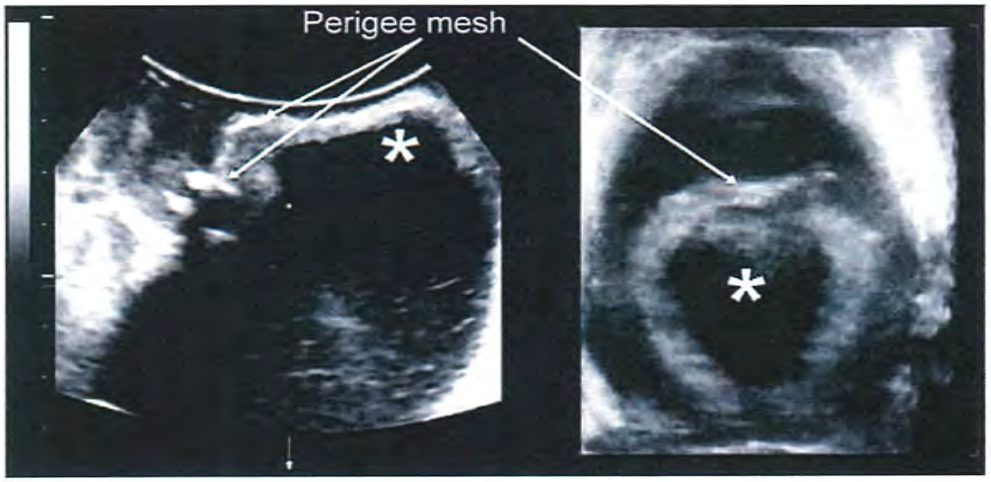
Cystocele recurrence 13%

⇒**Recurrence dorsal to the mesh with change in mesh axis**

⇒**Loss of support of the proximal part of the vagina**

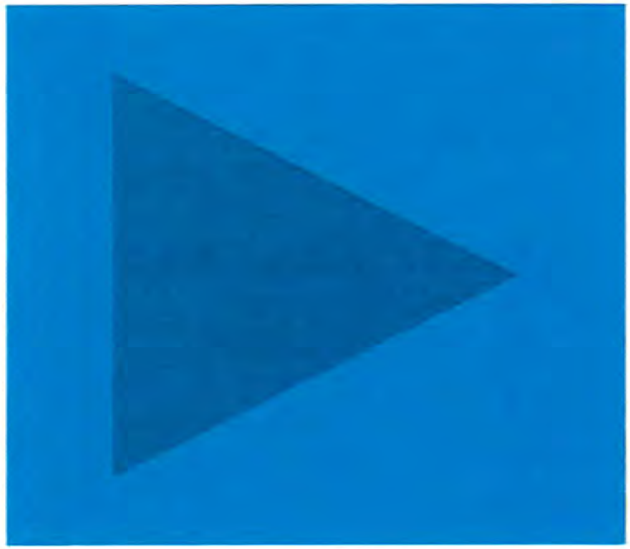
Patient with recurrent cystocele

- Dislodgment of superior arm
- Voiding dysfunction



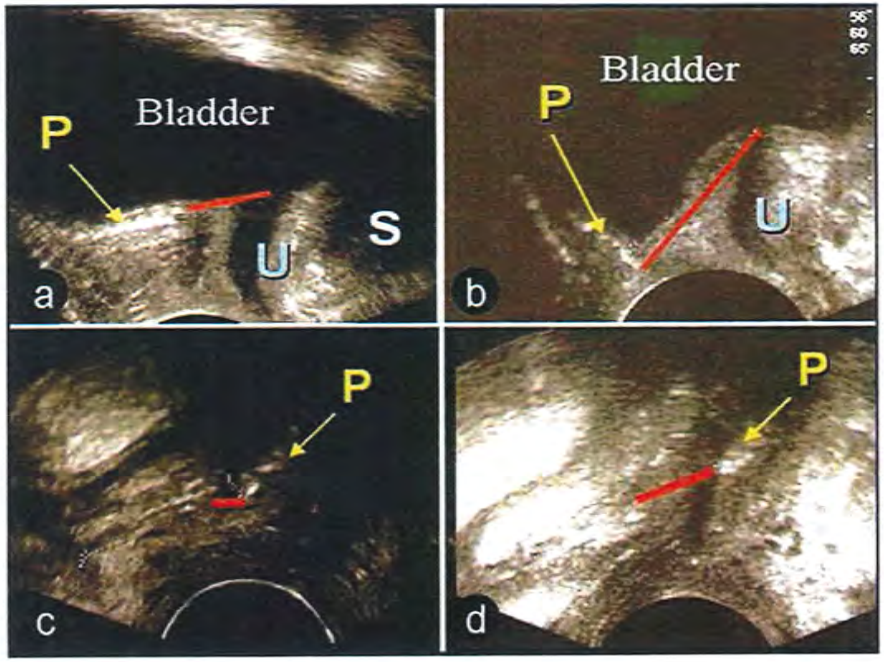
Video 2

Severe retraction of the anterior mesh with superior anchoring arm dislodgement and cystocle recurrence



Velemir L, Transvaginal mesh repair of anterior and posterior vaginal wall prolapse: a clinical and ultrasonographic study, Ultrasound Obstet Gynecol, 2009 (in press)

- 91 patients with anterior/posterior Prolift
- Control at ≥ 1 year follow up
- Distinction of patients with no, moderate (< 50%) or severe mesh retraction (≥ 50%) by transvaginal palpation
- POPQ
- Standardized US:
  - *Distance 1*, from the distal margin of the anterior mesh to the bladder neck
  - *Distance 2*, from the distal margin of the posterior mesh to the rectoanal junction
  - Mesh thickness



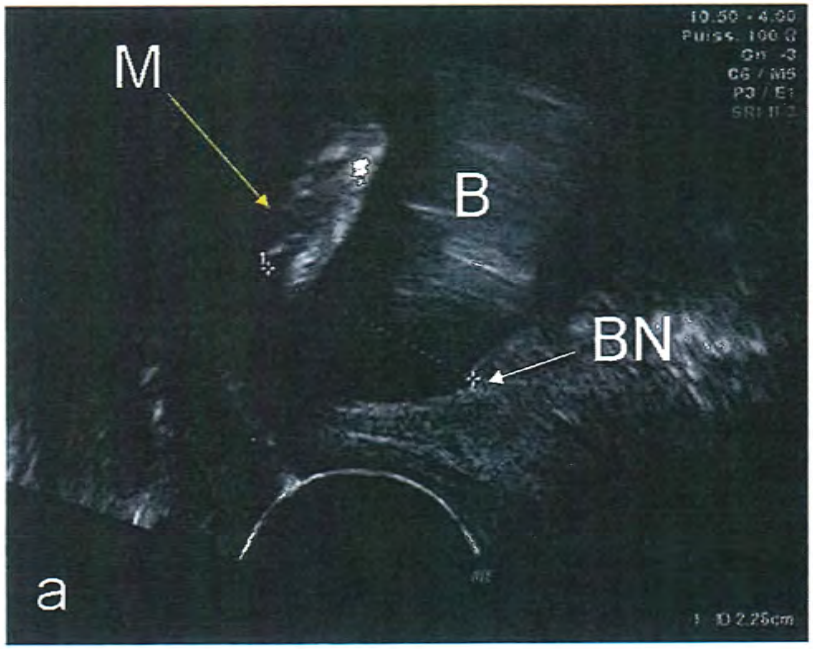
Results

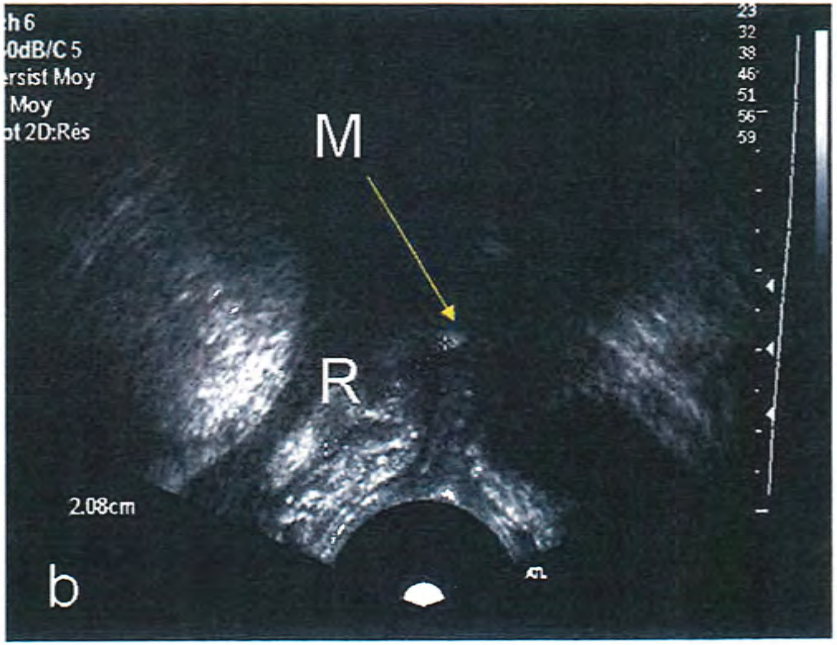
Velemir L, Ultrasound Obstet Gynecol, 2009 (in press)

- 75 anterior and 62 posterior meshes studied
- Follow up 17.9 months
- Patients with anterior recurrence presented significantly more often with severe anterior mesh retraction compared to patients without anterior recurrence (5/8 vs. 2/67, $p<0.001$) and also had an increased *distance 1* ($p<0.001$).
- Patients with posterior recurrence presented significantly more often with severe posterior mesh retraction compared to patients without posterior recurrence (3/4 vs. 3/58, $p<0.001$) and also had an increased *distance 2* ($p<0.01$). 107 patients
- Mesh thickness increase with mesh retraction

Recurrences after transvaginal mesh repair are associated with severe mesh retraction and loss of mesh support on the distal part of the vaginal walls.

Relation with POPQ and severe mesh retraction





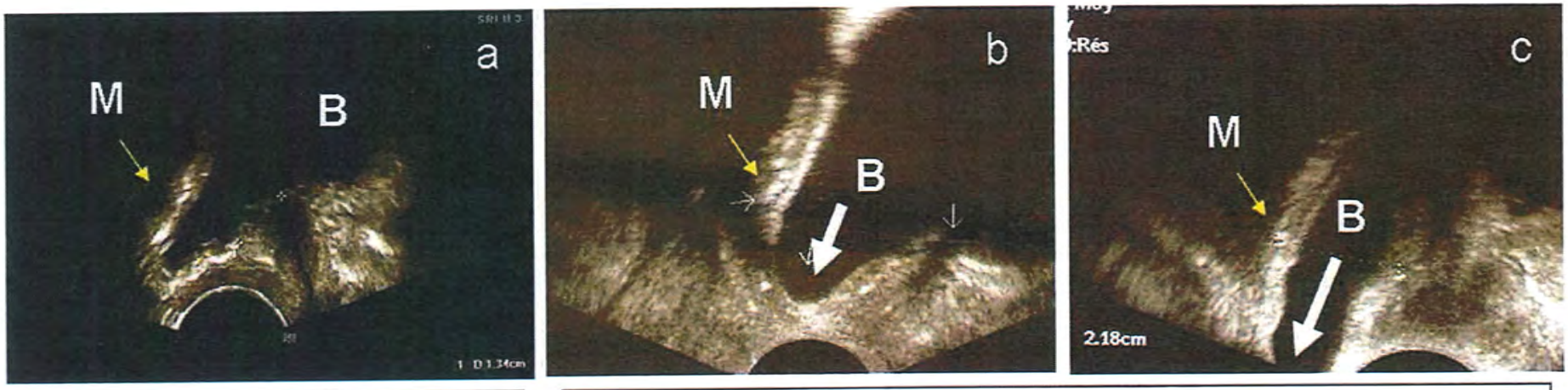
Severe anterior mesh retraction

Ba -1

Severe posterior mesh retraction

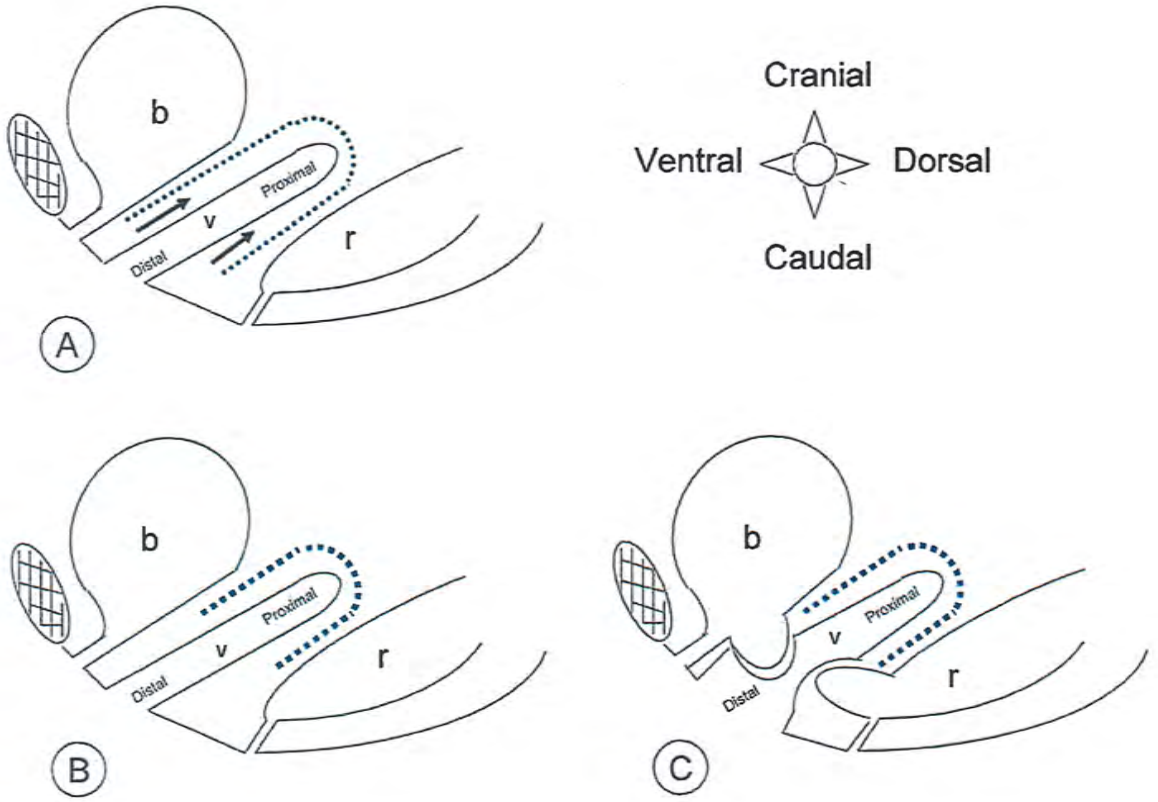
Bp -1

Anterior support and retraction



Moderate mesh retraction	Severe mesh retraction	
Ba - 2	**Ba - 1**	**Ba 0**

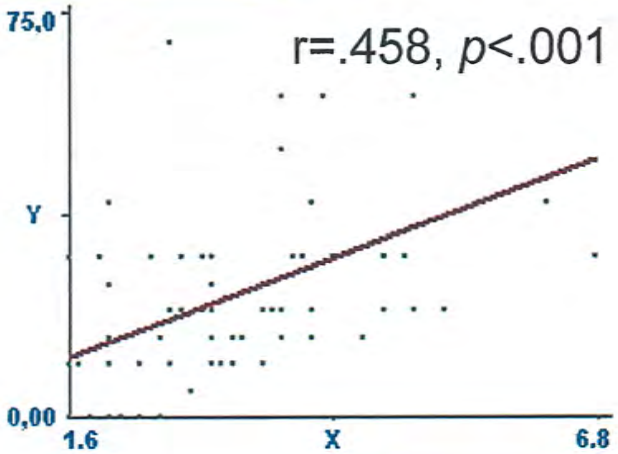
One mecanism of recurrence involved in cases with severe mesh retraction



Loss of support of the distal part of the vaginal walls

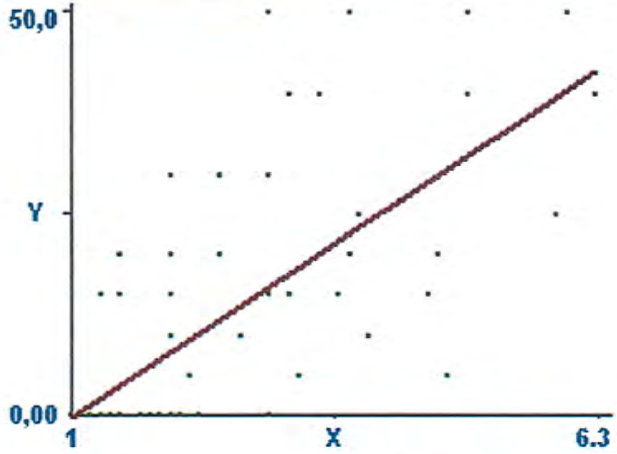
Significant correlation between clinical mesh retraction % and US mesh thickness

% of anterior mesh retraction



Maximal thickness of anterior mesh

% of posterior mesh retraction



Maximal thickness of posterior mesh

Velemir L, IUGA Annual Meeting Tai Pei 2008

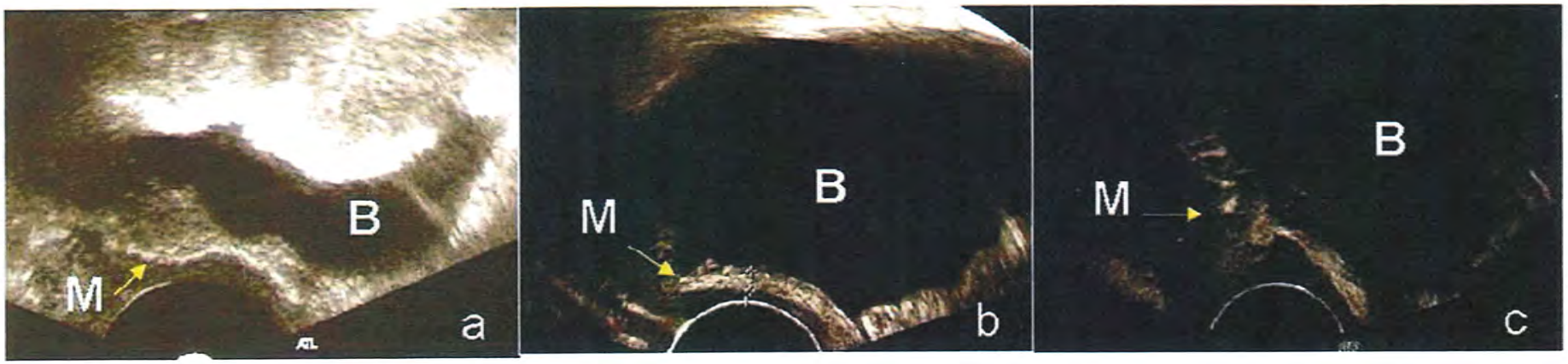
Thickness ≥ 5 mm with irregular aspect of the mesh at US is correlated sensitive shrinkage at vaginal examination

Se : 65%
Sp : 100%
Positive Predictive Value : 94.5%
Negative Predictive Value : 100%

Velemir L, IUGA Annual Meeting Tai Pei 2008

Correlation between thickness, aspect and retraction +/- pain

Anterior repair



Thin (1 mm) and regular	Thick (3mm) and regular	Thick (5 mm) and irregular
No retraction	**Retraction without pain**	**Retraction with pain**

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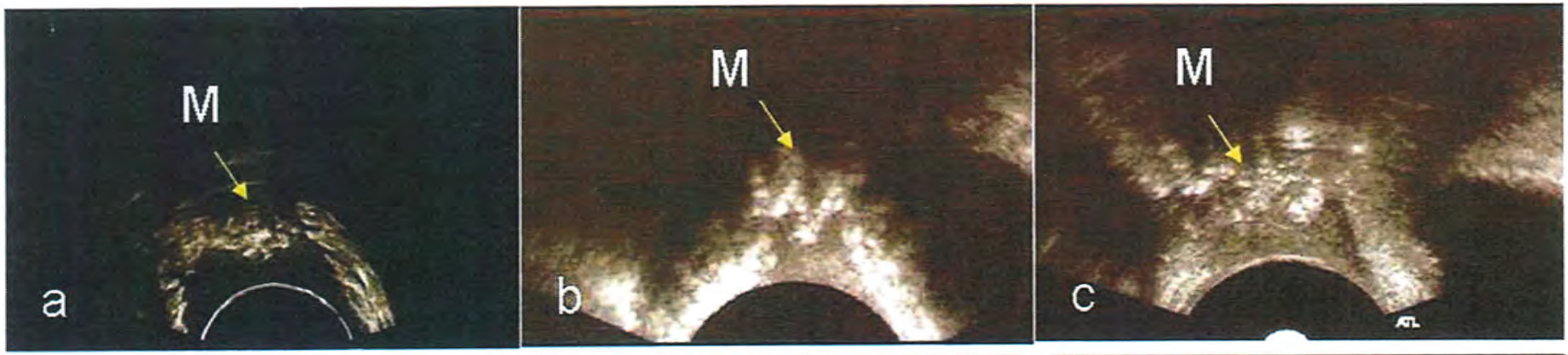
Correlation between thickness, aspect and retraction +/- pain

Posterior repair



Thick (3 mm) and regular	Thin (2 mm) and irregular	Thick (5 mm) and irregular
Retraction without pain		**Retraction with pain (VAS=5)**

Velemir L, IUGA Annual Meeting Tai Pei 2008

Severe mesh shrinkage after TVM

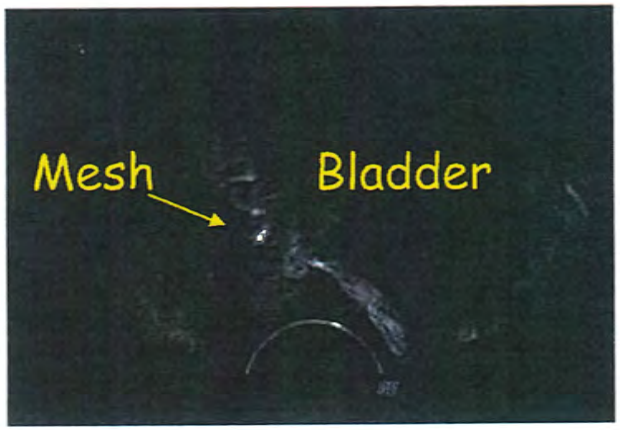
Pain and storage symptoms

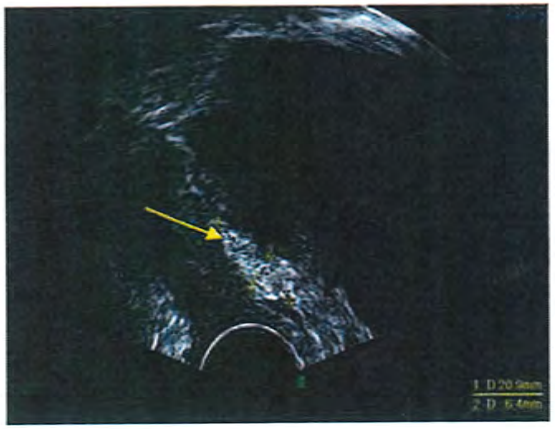
cystoscopy

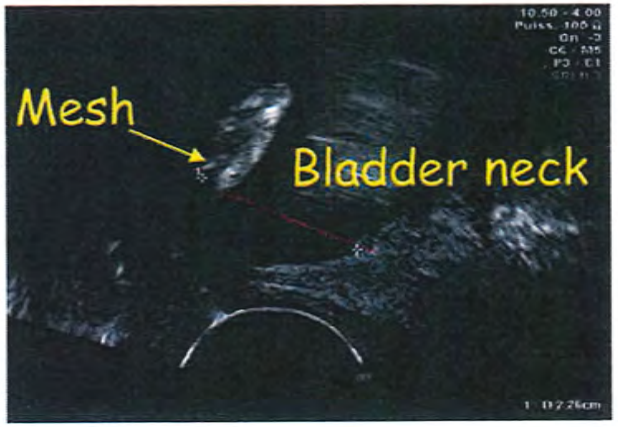
Perineal US scanning

Us assessment of mesh shrinkage

Irregular aspect	Thickness	Distance between caudal part of the mesh and anatomic landmarks







Velemir L, IUGA Annual Meeting Tai Pei 2008

How to prevent ?
Selection of the patients ?

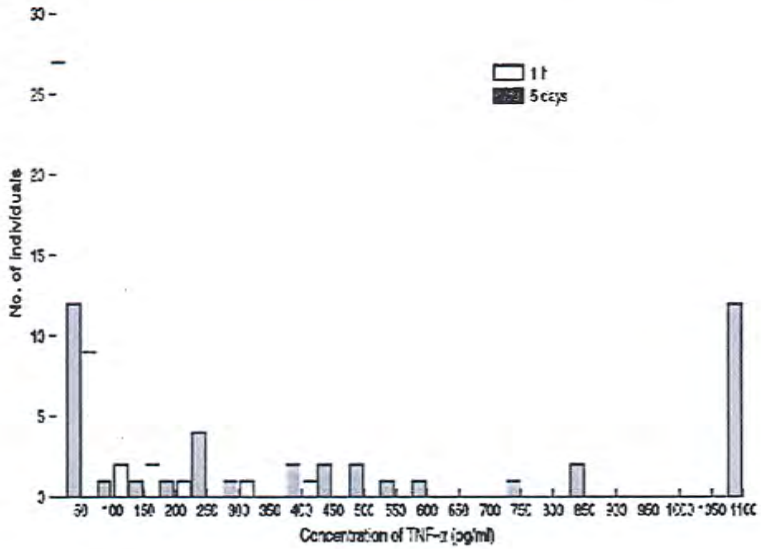
Original article

British Journal of Surgery 2003; 90: 114–120

Individual inflammatory response of human blood monocytes to mesh biomaterials

A. Schachtrupp[1,2], U. Klinge[1], K. Junge[1], R. Rosch[1], R. S. Bhardwaj[2] and V. Schumpelick[1]

- Assessment of monocyte–macrophage-derived proinflammatory and anti-inflammatory cytokines release after in vitro incubation with biomaterials
- The individual as an independent factor for the response to commonly used biomaterials.
- High and low responsder to biomaterials



How to prevent ?
Fixation of the mesh ?

The role of suture fixation on mesh contraction after abdominal hernia repair.
Sekmen U, Gurleyik G, Kayadibi H, Saglam A *J Invest Surg 2009 ;22:117-21*

- Comparison of the mesh contraction rate
- **Free mesh placement** vs. **mesh fixation**
- Rats with abdominal wall defect / Corners of the defect and prolene mesh marked with silver clips / Contraction rate assessed by:
  - *Radiological measurement*
  - *Measuring the mesh areas after harvesting abdominal patch*
- Distances between corner clips decreased by 31.5% vs 24.4% (p = .008)
- Mesh area decreased by 26.4% vs. 22% (p = .01)

⇒ *It seems important to keep the mesh in place until its incorporation into the surrounding tissue*

⇒ *Mesh contraction is minimized by suture fixation*

How to prevent ?
Expert opinion

- **To ask before surgery :**
  - Is it a good indication for vaginal mesh ?
  - How is the patient sexual function ?

- **To do during mesh placement :**
  - Avoid mesh folding or bending during mesh positioning => mesh should lie flat
  - Combine apical and lateral (**four corners**) suspension for the anterior graft
  - To pass the arms at the **more apical and distal part** of the ATFP to prevent folding ***anteriorly***
  - To pass through the SSL (NOT the coccygeous m.) ***posteriorly***, with final tension adjustement
  - Avoid excessive tension of the mesh
  - Use a vaginal packing *post operatively*

How to prevent ?

Avoid infection

1. Type I meshes (Amid classification)
2. Polypropylene meshes
3. Knitted Mono-filament
4. Large pore size
5. Rigorous asepsis
6. Prophylactic antibiotics
7. Reduce mesh exposition

Reduce mesh exposition

10 rules

1. Topical vaginal estrogens
2. Polypropylene mesh
3. Uterus preservation
4. Avoid "T incision" in case of hysterectomy: use retrograde dissection
5. Reduce vaginal incision length
6. Do NOT dissect between vagina and fascia
7. Use infiltration
8. Avoid colpectomy (only edges trimming)
9. Avoid ischemic suture (running sutures)
10. Avoid stitches between vagina and mesh

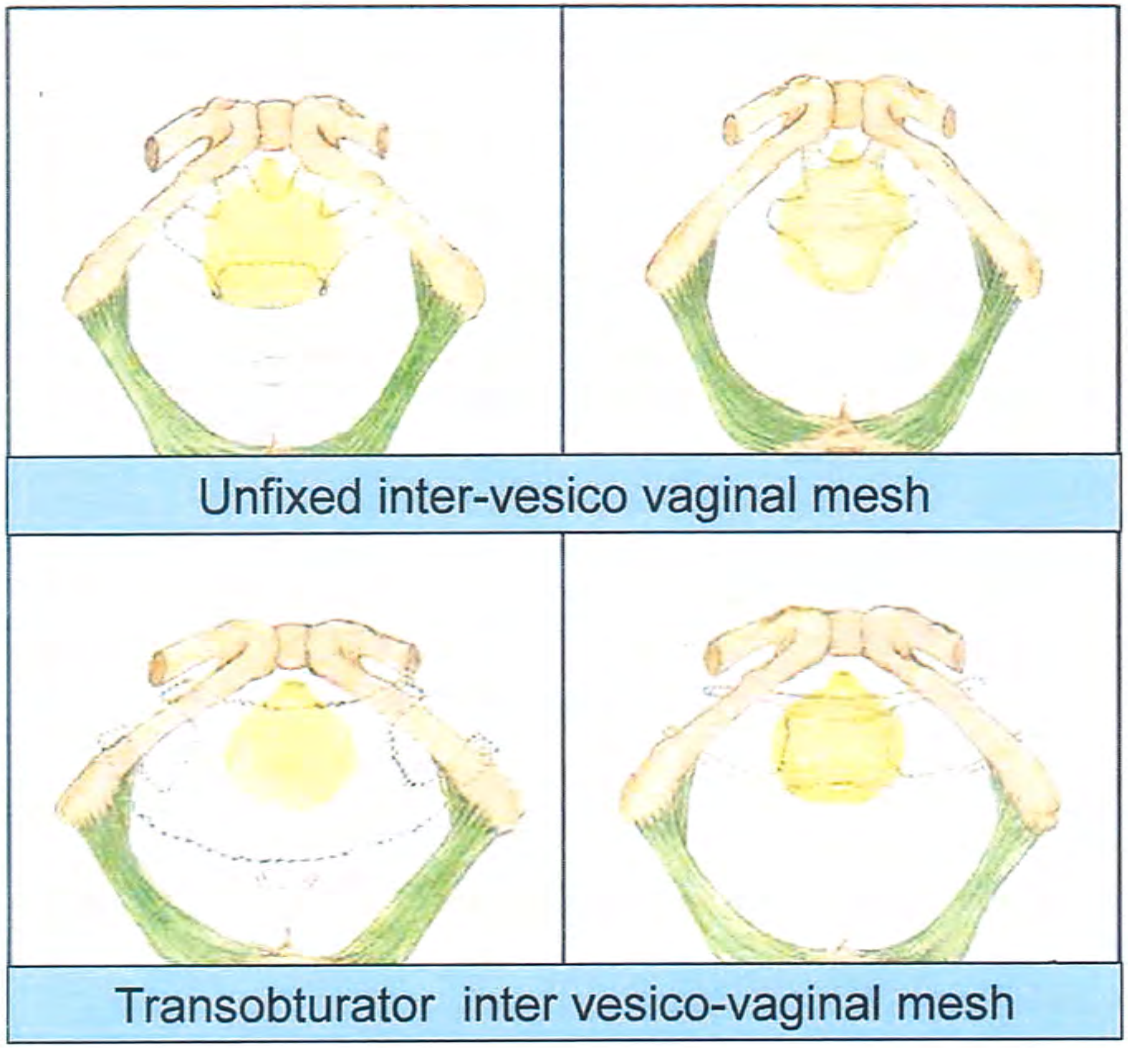
+ experienced surgeon

How to prevent ?

Modulate the mesh characteristics

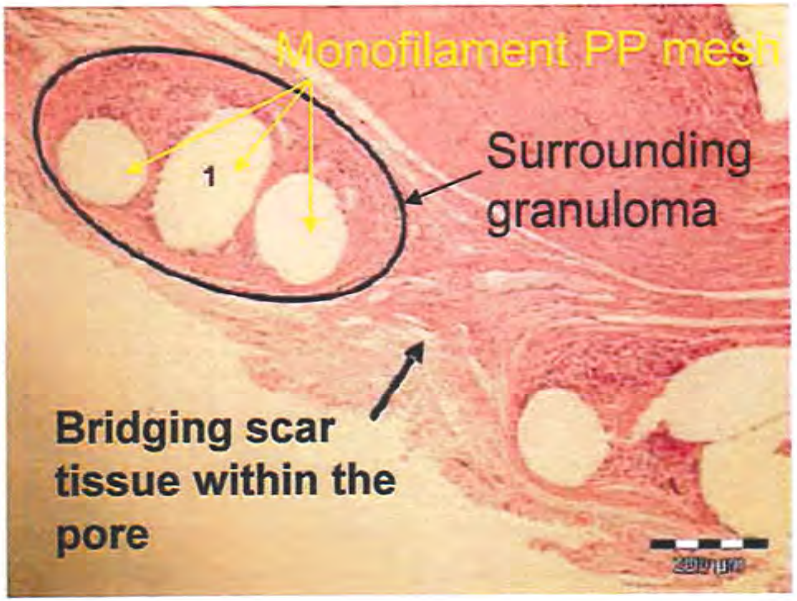
- Mesh size
- Pore size
- Quantity of materials
- Other:
  - Textile structure
  - Weave configuration
  - Fiber diameters

Use large mesh taking into consideration a global mesh shrinkage of 40%



Influence of mesh porosity on tissue reaction and mesh shrinkage

- In case of small pore size (<600-800 µm) the granuloma surrounding the polymer fiber and scar tissue may fill out completely the distance between the filaments
- ⇒ Inflammatory and fibrotic reaction leaving no space for further tissues ingrowth
- ⇒ Loss of elasticity
- ⇒ Support of the wound contraction and mesh shrinkage
- Larger pores filled mainly with local fat tissue preserving a proper elasticity of the device
- **Pore size appears to be of major importance in tissue reaction and for the biocompatibility of mesh structures**



Klinge U, Eur J Surg 1998
Klinge U, J Surg Res 2002
Mühl T, J Biomed Mater Res B Appl Biomater 2007

Influence of mesh quantity

- Light weight meshes may have better biocompatibility and may reduce patient complaints
- Less material = less host tissue response

O'Dwyer, Br J Surg 2005

Klinge U, J Biomed Mater Res 2002

Costello CR, Surgical Innovation, 2008

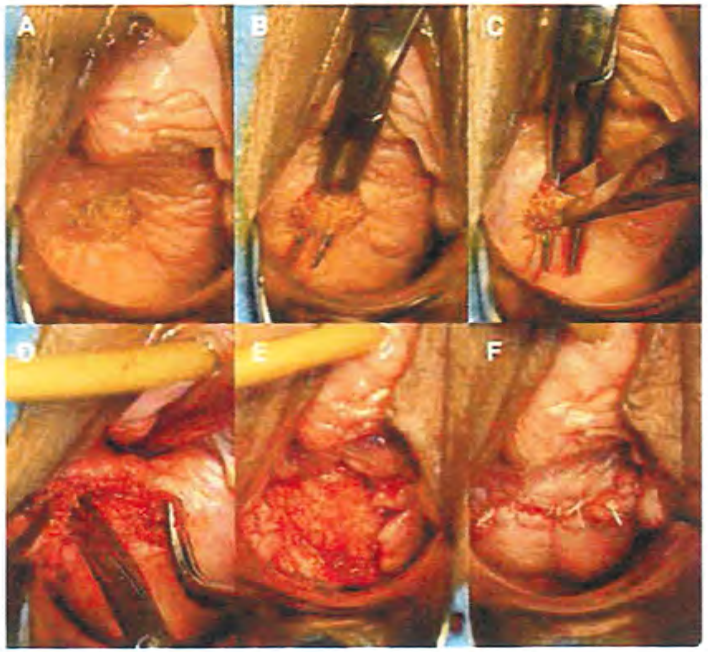
How to prevent ?

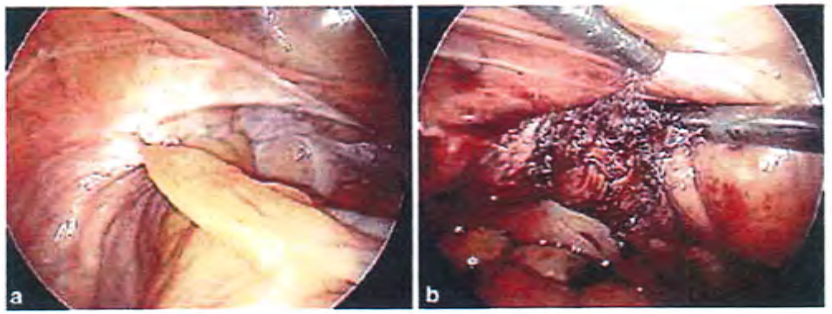
The future

- Mixed meshes (partly absorbable)
- Collagen coated mesh
- Antibiotic coated mesh
- Collagen mesh, Biomesh
- Long-lasting bioabsorbable mesh
- .....??

How to manage ?
Dyspareunia, shrinkage and bands

- Anti-inflammatory medication
- Local injections
- Physical therapy
- **Mesh excision**
  - Improves patients symptoms in most cases
  - Vaginaly
  - Laparoscopicaly





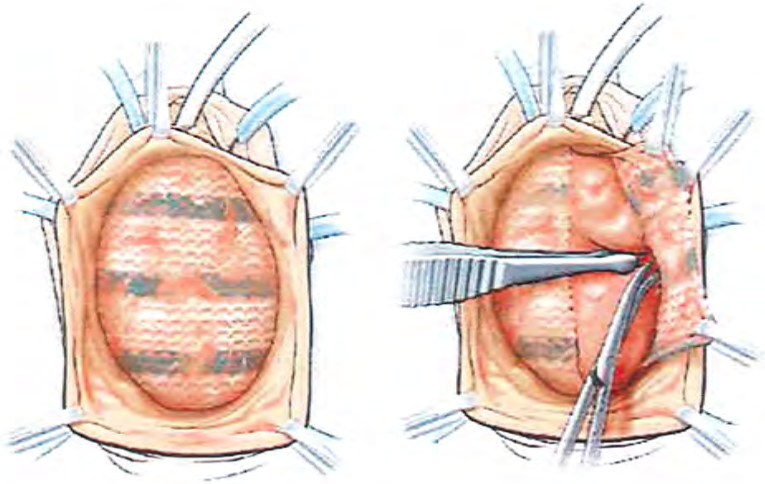
Margulies RU, AJOG 2008

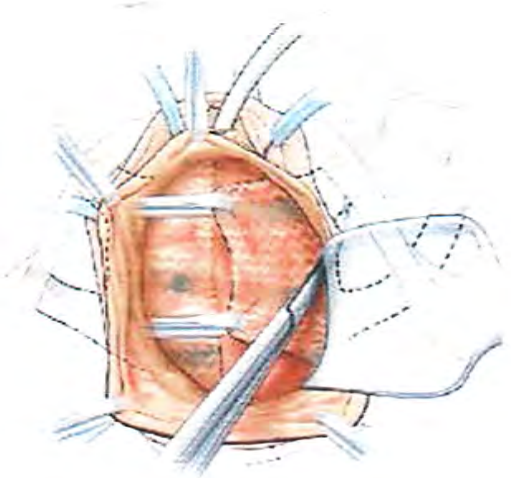
Sami Walid M, Arch Gynecol Obstet 2009

Mesh excision

Surgical technique

- **Infiltration** for hydrodissection and hemostasis
- Incision of the vaginal epithelium overlying the mesh
- Sharply **dissection between the vaginal epithelium and the mesh**
- **Graping of the mesh**
- Sharply **dissection between the mesh and the undelying layer** with Metzenbaum scissors
- **Transection of the mesh** with scalpel or heavy scissors
- **Excision of as much of the mesh as possible**
- **Closing of the vaginal epithelium under minimal tension**





Ridgeway B, AJOG 2008

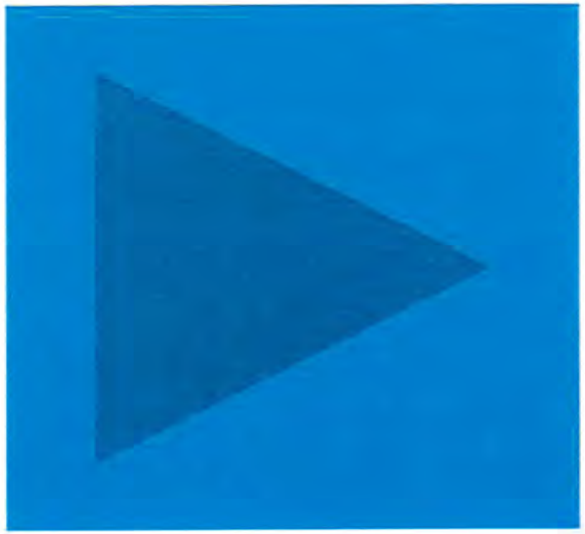
Mesh excision
Our experience

- ***121 surgical procedures performed for vaginal mesh complications in our unit from 1997 to 2006***
- **Most cases were referred !**

- Vaginal exposure 70.2%
- Pain 19.8%
- Infection 7.4%
- Visceral erosion 4.1%
- Dysuria 4.1%

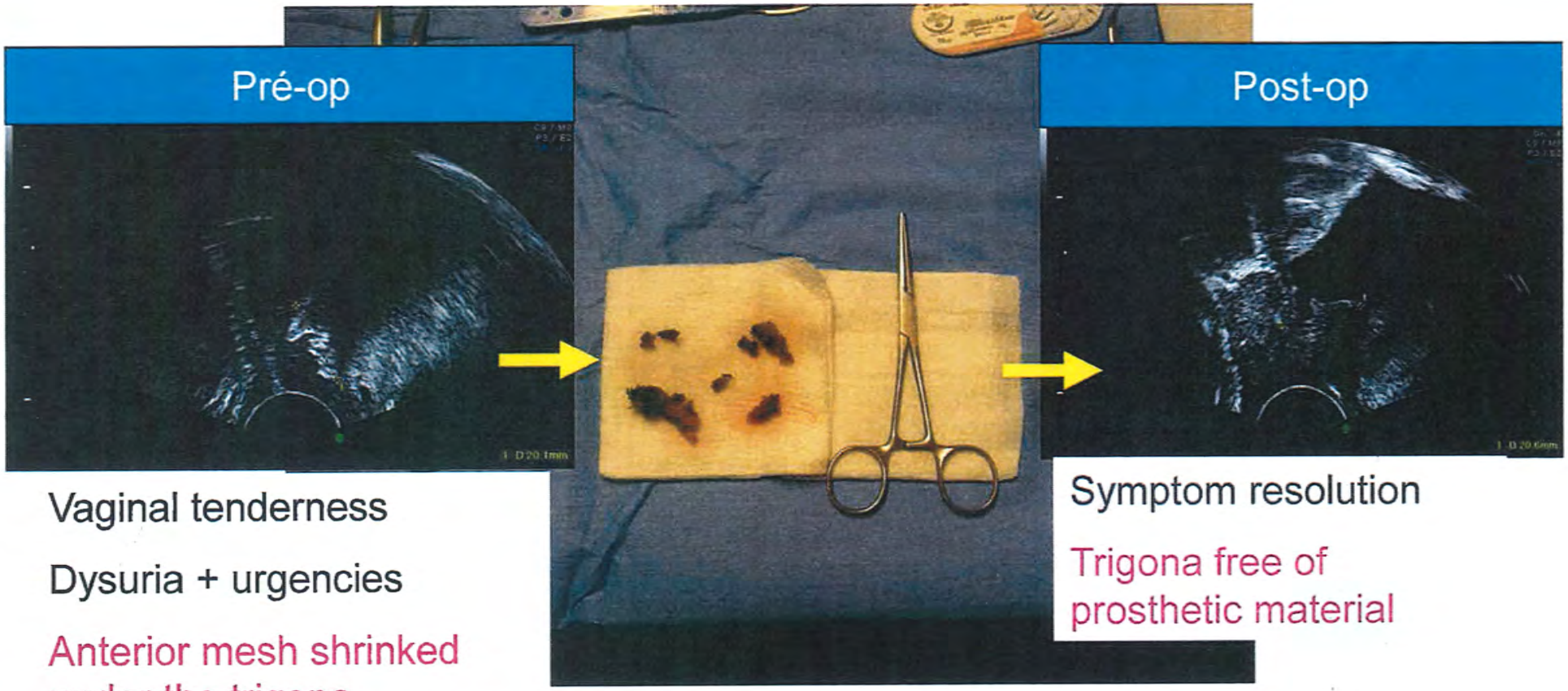
Video 3:

Complete dissection of the rectovaginal space after posterior transvaginal synthetic implant fixed bilaterally to sacrospinous ligament on account of vaginal erosion, patient pain and threatening mesh shrinckage compressing the rectum



Interest of ultrasonography in case of mesh removal

- Pre and postoperative cartography of the mesh



Vaginal tenderness

Dysuria + urgencies

Anterior mesh shrinked under the trigona

Symptom resolution

Trigona free of prosthetic material

Concerns raised by mesh removal

- Visceral extrusion of the mesh or severe infection as pelvic cellulites generally result in a difficult and complete excision of the graft
- Severe mesh retraction often require a complete removal of the mesh to relieve symptoms and avoid multiple procedures
- If the arms of the mesh are involved in the symptoms, the dissection has to be carried out quite laterrally so the arms can be transected as deep as possible
- Complete resection may induce prolapse recurrence and vaginal distortion/shortening which can be taken into consideration before and during the surgery

=> place and mode of concomitant prolapse repair ?

Conclusion

Mesh shrinkage

- Is real !
- Occurs during the scarring and remodelling process
- May result in a unpredictable way in severe complications including dyspareunia, pain and recurrence
- May require mesh removal
- Must be taken into consideration during patient councelling before surgery

Is a challenge for the next years !

⇒ Need for a better understanding

⇒ Need for a better assessment

⇒ Need for a better material behaviour (and techniques)

Thank you for your attention

Puy-de-Dôme, Clermont-Ferrand, France